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EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/242,202	NELSON ET AL.	
	Examiner	Art Unit	
	Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51 and 59-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33,36-51 and 59-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The Response to Restriction Requirement, Amendment, and Supplemental Amendment filed on January 4 and 16, 2002, respectively, have been entered and assigned as Paper #15 and 16.

Claims 4, 7-51, and 60-65 have been amended. It is noted that claims 52-59 have been canceled in the Preliminary Amendment (Paper #6), but resubmitted in the amended form in Paper #15, which will not be entered. Currently, claims 1-51, and 60-65 are pending in the application.

Sequence Rule Compliance

The specification and claims contain sequence disclosures (Pages 19, lines 10, 12; pages 47, primers 1 & 2) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2) but are not identified in the specification by sequence identifier numbers or present in the Sequence Listing. Applicant must provide sequence identifier where applicable, and if necessary a paper copy, a computer readable copy of the Sequence Listing and a statement that the content of the paper and computer readable copies are the same and; where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). Because this is the third notice for Sequence Rule Compliance, and the lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors, particularly in

sequence identifiers and their correspondence to the submitted Paper and Computer readable copy of the sequence listing. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification. A full response to this Office Action must include a complete response to the requirement for a Sequence Listing.

Election/Restrictions

Applicant's election of Group I with traverse in Paper No. 15 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 34, 35, 46-51 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 17.

Claims 1-33, 36-45, and 60-65 are under current examination.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows: An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Specification

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-33, 36-45, and 60-65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings, or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

Claims 1, 16, 23, and 44 recite "a human derived promoter or mammalian homolog thereof which is functional in a target tissue or target cells", given the broadest reasonable interpretation, the claims embrace a genus of human derived promoters and their mammalian homologs. However, the only human derived promoter disclosed is the RANTES promoter. The specification fails to teach the sequences, the structure-functional relationship of other human-derived promoters, or the common attribution of the genus of human derived promoters. Further, the specification fails to teach the sequences, structure-functional relationship of mammalian homolog of the human RANTES promoter, or the common attribution for the genus of mammalian homolog of the human-derived promoter. The term "human derived promoter or mammalian homolog thereof" is obvious generic to a considerable number of mammalian promoters, varying in the chemical structure and physical properties. The specification fails to provide an adequate description to teach the identifying characteristics and the structure-function relationship of the broad class of promoters with regard to their function as biologically active promoters functional in a target cell, and accordingly does not provide a reasonable guide for those seeking to practice the invention and sufficiently detailed to show that applicant was in possession of the claimed genus of the invention.

Claims 1, 16, 23, and 44 further recite "unique sites within an interrupted palindrome recognition sequence for restriction endonuclease". However, neither the sequences nor the chemical structures of the sites are disclosed in the specification. The specification teaches "*The sequence acceptance site is designed to directionally*

accept sequence-specific products from rtPCR-based cloning strategies via unique sequences within the interrupted palindrome recognition sequence for the Bgl I restriction endonuclease, which is incorporated into the PCR primers" (the last paragraph of page 17). However, the claims as written are not limited to Bgl I, they embrace any restriction endonuclease (RE), which is located within an interrupted palindrome recognition sequence. The term "unique sites within the interrupted palindrome recognition sequence" is obvious generic to a considerable number of RE sites, varying in the chemical structure and physical properties. The specification fails to provide an adequate description to teach the identifying characteristics and the structure-function relationship of the broad class of RE sites, and accordingly does not provide a reasonable guide for those seeking to practice the invention. The claimed invention fails to teach which REs are embraced by the claims. Therefore, the specification does not provide an adequate written description of the claimed invention in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 10, and 11 recite "a human-derived 3' splice sequence and a human-derived poly A sequence", "wherein the human-derived 3' splice and poly A sequence are derived from human growth hormone". Given the broadest reasonable interpretation, the claims embrace any 3' splice sequence and poly A sequences from any gene in any chromosome of any human cell type. Even limiting the sequences to human growth hormones, which could be secreted by variety of cell types, ranging from epithelial, endothelial cells to various stromal cells, to neuronal cells, thus, the 3' splice

region for these hormones would be varied. The specification teaches one human growth hormone 3' splicing sequence citing "*DeNoto et al*" (page 16, line 30), and SEQ ID Nos: 5-9 as preferred embodiments for the poly A sequences. As such, the specification fails to provide an adequate description to teach the identifying characteristics and the structure-function relationship of the broad class of human derived 3' splice sequences and poly A sequences, and accordingly does not provide a reasonable guide for those seeking to practice the invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

The Revised Interim Guidelines state "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (Column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES

WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (Column 2, page 71436). Considering the known or potentially unknown human-derived promoters, their mammalian homologs, unique sites for RE, human-derived 3' splice sequences, and poly A sequences embraced by these claims, the disclosed RANTES promoter, Bgl I site, or SEQ ID Nos: 5-11 are not the representative species of the genus.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of *all* human derived promoters and their mammalian homologs, *all* unique RE sites within an interrupted palindrome recognition sequenced, and all human derived 3' splice region. Therefore, only the described RANTES promoter, Bgl I RE site, and SEQ ID Nos: 5-11 meet the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-33, 36-45 and 60-65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for stimulating a specific immune response using a humanized polynucleotide vector pITL encoding a viral antigen does not reasonably provide enablement for stimulating a specific immune response using a

humanized polynucleotide vector comprising *any* human derived promoter or mammalian homolog thereof, *any* human-derived 3' splice sequence, and *any* human derived poly A sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

Claims 23 and 36 recite a method for expressing a target antigen and for stimulating a specific immune response to a target antigen in a mammal using the humanized polynucleotide vectors recited in claims 1-22. Claims 27 and 28 recite "a pharmaceutical composition" comprising a humanized polynucleotide vector. These claims clearly or implicitly state the intended use of the composition and methods. With respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. "WHEN A COMPOUND OR COMPOSITION CLAIM IS LIMITED BY A PARTICULAR USE, ENABLEMENT OF THAT CLAIM SHOULD BE EVALUATED BASED ON THAT USE". (MPEP 2164.01c) When analyzing the enabled scope of the claims, the intended use is to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the

specification. "A pharmaceutical composition" is defined as a composition for therapeutic use, to prevent, alleviate, treat, or cure a disease within the animal to which the substance is administered, therefore, will be evaluated by the standard. As such, the broadest reasonable interpretation of the claimed invention properly encompasses genetic vaccination for various infections and tumors, therefore, the claims will be evaluated by that standard.

In view of the guidance provided, the specification teaches a humanized vector pITL, table I describes the immune stimulatory effect achieved in various animal models using the instant invention for various viral infection. The specification further lays out plans for testing effects of a pITL-HER2/neo vector in animal models and human clinical trials, however, the data from these planned trials are not present in the instant specification. The specification is silent with regard to effects of any other humanized promoter/enhancer combination vectors in stimulating an immune response.

In view of the state of the art and the levels of the skill in the gene therapy and genetic vaccination art, it is well known that of paramount importance for the success of gene therapy is to deliver therapeutic genes to the sites of disease, to obtain a sustained expression at a significant level in a significant cell population. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, *Miller* (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene

therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). *Deonarain* (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). *Deonarain* reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). *Verma* (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of *Verma* indicate a resolution to vector targeting has not been achieved in the art (see entire article). *Verma* also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). *Crystal* (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

Moreover, 3' splice sequences are modulators of the gene expression, their function as to either up- or down-regulating gene expression varies from cell to cell, and from gene to gene. Promoters suitable for human gene therapy have been the focus for

developing a target gene-specific delivery system. *Nettelbeck et al* (Gene Ther 2000 April; 16:174-181) teach "SOME OF THE RECENTLY DESCRIBED EXPERIMENTAL GENE THERAPY PROTOCOLS DO INDEED MAKE USE OF NATURAL TISSUE-SPECIFIC PROMOTERS, BUT IN MANY INSTANCES THESE PROMOTERS SUFFER FROM A LACK OF ACTIVITY, SPECIFICITY OR BOTH." (the paragraph bridging page 174-175). "FREQUENTLY, HOWEVER, TISSUE-SPECIFIC OR OTHER SELECTIVE PROMOTERS ARE INEFFICIENT ACTIVATORS OF TRANSCRIPTION, WHICH SEVERELY LIMITS THEIR APPLICABILITY." *Miller and Whelan et al* (Human Gene Ther 1997 May; 8:803-815) teach " SOME CELLULAR PROMOTERS LARGELY RETAIN THE DESIRED SPECIFICITY WHEN PLACED IN VIRAL VECTORS;...NEVERTHELESS, IT IS NOT UNCOMMON THAT CELLULAR CIS-ACTING SEQUENCES LOSE SOME OR ALL OF THEIR ABILITY TO RESTRICT EXPRESSION APPROPRIATELY WHEN PLACED IN THE CONTEXT OF A VIRAL VECTOR." "THE CELLULAR ENVIRONMENT MAY HAVE A STRONG EFFECT ON PROMOTER ACTIVITY". Base on these teachings, it would be highly unpredictable to search and identify a known or unknown human-derived promoter, 3' splice sequence, and a poly A to determine if they would function properly together in a particular vector. *Verma* also indicates that appropriate enhancer-promoter sequences can improve expression, but that the "SEARCH FOR SUCH [USEFUL] COMBINATIONS IS A CASE OF TRIAL AND ERROR FOR A GIVEN CELL TYPE" (page 240, sentence bridging columns 2 and 3). Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for a specific combination of promoters, introns, and regulatory sequence in a particular carrier which would suitable for gene therapy. Although the instant specification provides a few preferred embodiments of the recited vectors, it is not enabled for its full scope because the specification fails to provide an adequate

description of the vector elements and an enabling disclosure for the functional effects of the combination of these elements.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving *in vivo* gene expression at therapeutic levels, in particular for the treatment of any and all infectious and malignant diseases, the lack of guidance provided by the specification as well as the absence of guidance for all possible combination of vector components with regard to their function in gene therapy, and the breadth of the claims directed to the use of numerous therapeutic gene/promoter/enhancer combinations, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-33, 36-45, and 60-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 16, 23, and 44 recite "unique sites within an interrupted palindrome recognition sequence for restriction endonuclease". However, neither the name, nor sequences of the sites are disclosed in the specification. In page 17, the last paragraph of the specification, it states "*The sequence acceptance sit is designed to directionally accept sequence-specific products from rtPCR-based cloning strategies via unique sequences within the interrupted palindrome recognition sequence for the Bgl I*

restriction endonuclease, which is incorporated into the PCR primers". However, the claims as written are not limited to Bgl I site, they embrace any restriction endonuclease (RE) which is located within an interrupted palindrome recognition sequence. Because it is unclear which RE sites are encompassed by these claims, for examining purpose, the claims would be treated as they recite a site for *any* restriction endonuclease.

The claims are vague and indefinite because they recite "said vector lacking nucleic acid sequences encoding vector-derived polypeptides". The term "lacking" is not defined by the claim, and encompasses ranges from less than full-length to devoid of the recited polypeptide-coding region, the specification does not provide a standard for ascertaining the requisite degree of "lacking", and one of the skilled in the art would not be reasonably apprised of the scope of the invention.

The claims are vague and indefinite because the claim recitation "cDNA target products", the specification does not define the term, it is unclear what the term means in the context of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-3, 7, 10, 16-19, 23-31, 36-37, 41-44, and 65 are rejected under 35 U.S.C. 102(e) as being anticipated by *Roop et al* (US 6,143,727).

These claims are directed to a polynucleotide vector comprising a human derived promoter or mammalian homolog thereof, which is functional in a target cell, operably linked to a sequence acceptance site via a RE site, wherein the vector lacking nucleic acid sequences encoding vector-derived polypeptides, wherein the vector further comprises a nucleic acid sequence which allows for selection of recombinant plasmid but lacking an antibiotic resistance encoding sequence, wherein the vector encodes a tumor associated genetic derangement, a tumor antigen, an bacterial or viral antigen, wherein the target cells are human, wherein the vector further comprises a human-derived 3' splice sequence and a poly A sequence. Claims 23-26 are further directed to a method for expressing the vector in cells in *vivo* or *ex vivo* or stimulating an immune response in a mammal using the vector via muscle or skin routes with an expression enhancing agent, wherein the cells are myocytes or professional antigen presenting cells, wherein the method generates antigen specific cytotoxic lymphocytes to the tumor antigen. Claims 27-31 are directed to a composition and a kit comprising the vector and an expressing enhancing agent. The specification defines the "sequence acceptance site" as "cloning site" for accepting sequences from rtPCR (page 17, the last paragraph).

Roop et al teach a polynucleotide vector, having minimal vector derived polypeptide-coding sequence, comprising a human or mammalian epidermal keratin promoter which function in human keratinocytes, a sequence acceptance site (a nucleic

acid cassette, column 5, lines 55-67), a CAT reporter coding sequence (selectable marker, column 3, line 66), and a keratin-derived 3' splice region including a poly A sequence (claims 1, 3, 4; paragraph bridging columns 3 & 4; column 8, lines 4-6). *Roop et al* further teach that the nucleic acid cassette encodes tumor suppressors (p 53, ras, etc.), tumor, viral, bacterial and parasitic antigens, for example (column 6, lines 2-18). *Roop et al* go on to teach a method of treating skin cancer in a mammal comprising administering the expression vector at or directly around the site of a skin cancer cell (claim 1) or by intramuscular injection (myocytes, column 20, line 29), or by ex vivo transformation and then skin graft (column 19, Cell Transformation). *Roop et al* also teach administering an expression enhancing agent, such as liposome (column 20, lines 37-43). Professional antigen presenting cells are present in the skin cancer sites, and the administering of the recited expression vector would generate a tumor specific cytotoxic lymphocytes, thus, *Roop et al* anticipate the instant claims.

Claims 1-3, 7-9, 15, 27, 29, and 30, are rejected under 35 U.S.C. 102(e) as being anticipated by *Carrano et al* (US 6,197,755).

These claims are directed to a polynucleotide vector comprising a human derived promoter or mammalian homolog thereof, which is functional in a target cell, operably linked to a sequence acceptance site via a RE site, wherein the vector lacking nucleic acid sequences encoding vector-derived polypeptides, wherein the vector further comprises an origin for replication and a nucleic acid sequence which allows for selection of recombinant plasmid, wherein the origin for replication is colE1, wherein the

vector encodes a tumor associated genetic derangement, e.g. p53, a tumor antigen, an bacterial or viral antigen, wherein the vector further encodes an cytokine such as interleukins and GM-CSF, wherein the target cells are human. Claims 23-26 are further directed to a method for expressing the vector in cells or stimulating an immune response in a mammal using the vector via muscle or skin routes with an expression enhancing agent, wherein the cells are myocytes or professional antigen presenting cells, wherein the method generates antigen specific cytotoxic lymphocytes to the tumor antigen. Claims 27-31 are directed to a composition and a kit comprising the vector and an expressing enhancing agent. The specification defines the "sequence acceptance site" as "cloning site" for accepting sequences from rtPCR (page 17, the last paragraph).

Carrano et al teach a polynucleotide vector, having minimal vector derived polypeptide-coding sequence, comprising a promoter that could be derived from human (column 6, lines 37-39), a PCR sequence acceptance site (Example 41), a colE1 origin (column 34, line 62-63), and an antibiotic selection sequence (figs 1 & 4a). *Carrano et al* further teach that the cloning site encodes a viral antigen (claim 12), and an oncogene (claim 15), for example, and further encodes a cytokine (column 7, lines 1-11). *Carrano et al* go on to teach a method of generating an immune response in a individual comprising introducing the vector by intramuscular injection (myocytes, claims 1, 2), and by skin (claim 8), because professional antigen presenting cells are present in the dermal sites, and the administering of the recited expression vector encoding a tumor gene would generate a tumor specific cytotoxic lymphocytes. *Carrano* et al also teach

administering a genetic vaccine facilitator agent, such as liposome and urea (column 2, lines 2-10). Thus, *Carrano et al* anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 7-9, 15-21, 23-31, 36, 37, and 41-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Carrano et al* (US 6,197,755) as applied to claims 1-3, 7-9, 15-21, 27, 29, 30, 36, 37, and 41-44 above, and further in view of *Eastman et al* (US 6,103,470).

Claims 16 and 23 recite that said vector lacks an antibiotic resistance encoding nucleic acid sequence.

The teaching of *Carrano et al* as described above fails to teach a vector selection marker other than an antibiotic resistance sequence (Amp and Kana).

Eastman et al teach gene delivery vectors containing antibiotic resistance would pose a problem to humans as the resistance is imparted, and transmission of the gene to potential pathogens may be of a problem (paragraph bridging columns 2 & 3), thus, they offered other ways of vector selection (abstract, claims 10 and 11).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Carrano et al* by simply deleting

the antibiotic resistance sequence in the vector as taught by *Eastman et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because it could avoid the potential problem of antibiotic resistance in humans. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-3, 7-9, 15-21, 23-31, 36, 37, and 41-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Carrano et al* (US 6,197,755) and *Eastman et al* (US 6,103,470) as applied to claims 1-3, 7-9, 15-21, 23-31, 36, 37, and 41-44 above, and further in view of *Zurr et al* (US 5,648,235).

Claim 15, 16 and 23 recite an optional internal ribosomal entry site in the humanized vector.

The teaching of *Carrano et al* and *Eastman et al* as described above fails to teach a multi-cloning site comprising an internal ribosomal entry site (IRES).

Zurr et al teach a method for production of desired proteins, uses an "on-off translation mechanism", i.e. including an IRES in the vector system (columns 3, lines 32-34) they go on to teach that such mechanism can be better exploited to obtain gene products in significant amounts and in a selective manner (column 3, lines 50-61).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Carrano et al* and *Eastman et al* by simply combining a IRES in the expression vector as taught by *Zurr et al* with a reasonable expectation of success. The ordinary skilled artisan would have been

motivated to modify the claimed invention because it could gain better control of the expression of the gene of interest. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-3, 7, 10, 16-19, 23-31, 36-44, and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Roop et al* (US 6,143,727) as applied to claims 1-3, 7, 10, 16-19, 23-31, 36-38, 41-44, 65 above, and further in view of *Danko et al* (Gene Ther 1994;1:114-121).

Claims 38-40 recite to administer an expression enhancing agent prior to administerion of the vector, wherein the agent is a myotoxic agent, a bupivacaine-HCl.

The teaching of *Roop et al* as described above fails to teach a myotoxic agent particularly bupivacaine-HCl as an expression enhancer.

Danko et al teach a method for enhancing in vivo gene expression in muscle by pre-treating muscle with various myotoxic agents such as bupivacaine (see abstract, right column).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Roop et al* by simply combining the myotoxic agent in the composition as taught by *Danko et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the method could improve the intramuscular gene delivery. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed. Claims 4-6, 12-14, 22, 45, and 60-64 are free of the cited art of record, but they are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Clark can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
February 1, 2002

JAMES KETTER
PRIMARY EXAMINER